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(54) Title: METHODS AND APPARATUS FOR PARTICLE PRECIPITATION AND COATING USING NEAR-CRITICAL AND SUPERCRITICAL ANTISOLVENTS
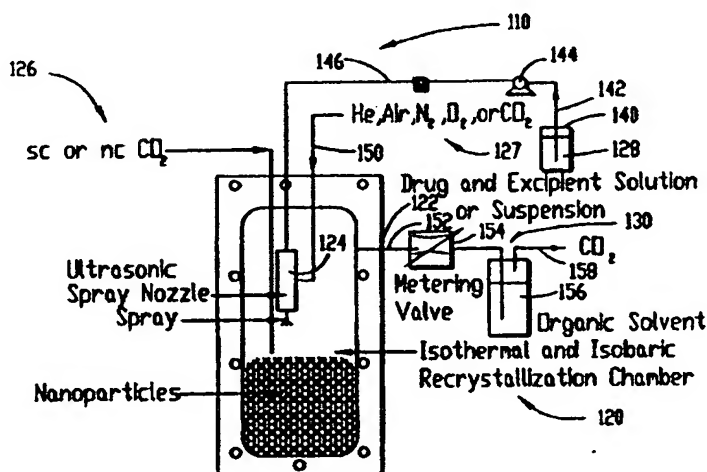
(57) Abstract

Improved method and apparatus (110) for particle precipitation and coating using near- or supercritical fluid conditions. A fluid dispersion (128) having a continuous phase dispersant and at least one precipitable substance therein is contacted with a supercritical fluid (SCF) antisolvent (126) so as to generate focused high frequency antisolvent sonic waves, breaking up the dispersion into extremely small droplets. The enhanced mass transfer rates between the droplets and the antisolvent causes precipitation of very small particles on the order of 0.1-10 microns. In coating processes, a turbulent fluidized flow of core particles is created using SCF antisolvent in an enclosed zone. The core particles are contacted therein at or near supercritical conditions by fluid dispersion containing a dispersant and together with a precipitable substance. The antisolvent depletes the dispersant and the substance is precipitated onto fluidized particles.

METHODS AND APPARATUS FOR PARTICLE PRECIPITATION AND COATING USING NEAR-CRITICAL AND SUPERCRITICAL ANTISOLVENTS

5   CROSS REFERENCE TO RELATED APPLICATIONS

The benefit of the following Provisional Patent Applications are claimed: Serial No. 60/012,593, filed March 1, 1996, and entitled RECRYSTALLIZATION OF NANOPARTICLES OF SUBSTANCES SOLUBLE IN AN ORGANIC SOLVENT; AND COATING OF MICROPARTICLES INSOLUBLE IN AN ORGANIC

10   SOLVENT WITH A SUBSTANCE SOLUBLE IN THE SAME ORGANIC SOLVENT, and Serial No. 60/012,592, filed March 1, 1996 entitled PRODUCTION OF PHARMACEUTICAL DRUG PRODUCTS BY LYOPHOBIC PRECIPITATION USING NEAR- AND SUPERCRITICAL FLUIDS. This is also a continuation-in-part of application Serial No. 08/723,463, filed October 9, 1996.

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FIELD OF THE INVENTION

The present invention relates to a method and an apparatus for extremely small particle precipitation, wherein a fluid dispersion containing a substance to be precipitated is contacted with a supercritical fluid (SCF) antisolvent such as carbon

20   dioxide under near-or supercritical temperature and pressure conditions for maximizing small particle formation. The invention provides spray techniques wherein the interphase mass transfer rate is maximized between small droplets of the dispersion and antisolvent so as to generate precipitated particles having an average diameter of from about 0.1-10 µm. The invention also includes supercritical fluid coating techniques

25   wherein fluidized core particles are coated with precipitated particles in a SCF antisolvent precipitation chamber.

DESCRIPTION OF THE PRIOR ART

A number of industries have experienced a long-felt need for particle

30   micronization and nanonization. The need for an apparatus or method capable of producing sub-micron and nano-sized particles is particularly pronounced in the field of pharmaceutics. Conventional techniques for particle-size reduction currently practiced suffer from many disadvantages. These conventional methods involve either mechanical comminution (crushing, grinding, and milling) or recrystallization of the

35   solute particles from liquid solutions. The limitations of mechanical comminution for particle-size reduction are the shock sensitivity associated with the solid, thermal degradation due to heat generation during mechanical comminution, lack of brittleness

Patent No. 5,360,478 to Krukonis et al.; U.S. Patent No. 5,389,263 to Gallagher et al.).
See also, PCT Publication WO 95/01221 and U.S. patent No. 5,043,280 which describe
additional SCF particle-forming techniques.

In the RESS process, a solute (from which the particles are formed) is first
solubilized in supercritical CO_2 to form a solution. The solution is then sprayed through
a nozzle into a lower pressure gaseous medium. Expansion of the solution across this
nozzle at supersonic velocities causes rapid depressurization of the solution. This rapid
expansion and reduction in CO_2 density and solvent power leads to supersaturation of
the solution and subsequent recrystallization of virtually contaminant-free particles.
The RESS process, however, is not suited for particle formation from polar compounds
because such compounds, which include drugs, exhibit little solubility in supercritical
CO_2. Cosolvents (e.g., methanol) may be added to CO_2 to enhance solubility of polar
compounds; this, however, affects product purity and the otherwise environmentally
benign nature of the RESS process. The RESS process also suffers from operational
and scale-up problems associated with nozzle plugging due to particle accumulation in
the nozzle and to freezing of CO_2 caused by the Joule-Thompson effect accompanying
the large pressure drop.

The relatively low solubilities of pharmaceutical compounds in unmodified
carbon dioxide are exploited in the second process wherein the solute of interest
(typically a drug, polymer or both) is dissolved in a conventional solvent to form a
solution. The preferred ternary phase behavior is such that the solute is virtually
insoluble in dense carbon dioxide while the solvent is completely miscible with dense
carbon dioxide at the recrystallization temperature and pressure. The solute is
recrystallized from solution in one of two ways. In the first method, a batch of the
solution is expanded several-fold by mixing with dense carbon dioxide in a vessel.
Because the carbon dioxide-expanded solvent has a lower solvent strength than the
pure solvent, the mixture becomes supersaturated forcing the solute to precipitate or
crystallize as microparticles. This process was termed Gas Antisolvent (GAS)
recrystallization (Gallagher et al., 1989).

The second method involves spraying the solution through a nozzle into
compressed carbon dioxide as fine droplets. In this process, a solute of interest
(typically a drug, polymer or both) that is in solution or is dissolved in a conventional
solvent to form a solution is sprayed, typically through conventional spray nozzles,
such as an orifice or capillary tube(s), into supercritical CO_2 which diffuses into the
spray droplets causing expansion of the solvent. Because the CO_2-expanded solvent
has a lower solubilizing capacity than pure solvent, the mixture can become highly
supersaturated and the solute is forced to precipitate or crystallize. This process has
been termed in general as Precipitation with Compressed Antisolvents (PCA)(Dixon,

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Whistle-type devices have been used to generate high-intensity sound waves in both air and liquids. A practical upper frequency for applications using air is approximately 30 kHz. Using helium or hydrogen, such whistles are capable of generating ultrasonic energy in air up to 500 kHz. It is generally recognized in the field
5   that the effectiveness of the device in an application correlates with the frequency (or inversely with the wavelength). The efficiency (ratio of radiated power to the power delivered to the transducer) for such has been reported between < 5% to 14%. It is also recognized in the field that the effectiveness of the device does not necessarily correlate with its efficiency. In other words, a low-efficiency nozzle can be highly effective in
10   producing desired droplet sizes.

Whistles for generating sound waves in liquid have also been developed for industrial use. Since the velocity of sound is considerably higher in liquids than in gases, jet velocities equal to the velocity of sound are impractical in liquids. The whistles of W. Janovsky and R. Pohlmann (Zeitschrift für Angewandte Physik, 1, 222,
15   1948) operate on the jet-edge principle, wherein a high-pressure jet of the liquid or liquids is impinged on the edge of a thin plate which is mounted at the displacement nodes. The plate vibrates in flexure at resonance producing low-frequency waves, typically on the order of magnitude of 5000 Hz. Such "liquid whistles" have been used to produce emulsions or dispersions of one dense medium in another dense medium
20   (oil/water, mercury/water, etc.)

In many instances, especially in the pharmaceutical industry, it is desired to coat core particles or medicaments. Generally, such coating has been carried out using techniques such as electrolysis, vapor deposition, and fluidized bed or air suspension techniques. However, these methods all suffer from various drawbacks, e.g., the
25   difficulty in maintaining aseptic conditions, the inability to generate extremely fine particles for coating purposes and solvent emission control.

SUMMARY OF THE INVENTION

The present invention provides improved near- or supercritical fluid processes
30   for the precipitation of extremely small particles having average diameters (inferred from SEM photographs) on the order of from about 0.1-10 µm and most preferably up to about 0.6 µm. The methods of the invention find particular utility as methods for particle micronization and nanonization, particularly in the field of pharmaceutics. However, the methods of the invention can also be used in other fields such as those
35   related to foods, chemicals, polymers, pesticides, explosives, coatings and catalysts wherein benefits are obtained from a decrease in particle sizes and concomitant increases in particle surface areas.

passageway and through a second passageway outlet proximal to the first fluid dispersion outlet. The passage of such an energizing gas stream through the second outlet generates high frequency waves of the energizing gas adjacent the first passageway outlet in order to break up the fluid dispersion into extremely small

5   droplets. This causes the antisolvent in the precipitation zone to deplete the dispersant and rapidly precipitate small particles of the substance.

The preferred process of the invention involves deliberate generation of high energy sonic waves (Type II waves) in addition to and substantially independent of any impaction and frictional forces typical of prior art nozzles (Type I waves). Type II

10   sonic waves may be generated in the energizing gas stream or in the dispersion itself. In the former situation, specialized nozzles as described below are used, and in the latter, a starting dispersion may be sprayed onto a sonicating surface coupled to a transducer (e.g., piezoelectric, magnetostrictive, or electromagnetic), and the resultant particles are contacted with turbulent SCF fluid.

15   In preferred forms, the specialized nozzle is of the type commercialized by Sonimist of Farmingdale, NY as Model 600-1. This nozzle includes an elongated body presenting a central tube which serves as the primary spray nozzle for the dispersions of the invention. The nozzle structure also includes a secondary passageway in surrounding relationship to the central tube for passage of the energizing gas along the

20   length of the central tube and out the nozzle outlet. The secondary passageway for the energizing gas is configured to present a converging section defining a restricted throat, with a diverging section downstream from the throat and leading to the nozzle outlet. In addition, the diverging portion of the secondary passageway is equipped with a radially expanded, annular resonator cavity for reflecting sound waves. The outlet end

25   of the central tube is located downstream of the constricted throat.

Use of nozzles of this type serves to generate and focus the preferred high frequency sonic waves of energizing gas which has been shown to maximize the production of extremely small dispersion droplets in the precipitation zone, thereby leading to the precipitation of the very small particles of the invention. The frequency

30   of the generated waves of energizing gas could range anywhere from 0.5 kHz to 300 kHz, and more preferably from about 10-100 kHz. It is believed that the inherent kinetic energy of the energizing gas stream is converted to acoustic energy by virtue of passage of the energizing gas stream through the restricted throat, resonator cavity and outlet of the nozzle. Generally, at least about 1% (more preferably from about 2-14%)

35   of the kinetic energy of the energizing gas stream is converted to acoustic energy.

In preferred forms, the energizing gas is the same as the selected antisolvent, and in most cases carbon dioxide is used both as the antisolvent and energizing gas. More broadly however, the energizing gas may be selected from the group consisting of air,

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method involves lyophobic precipitation of medicaments which may be performed in a batch or semi-batch mode.

In preferred forms, the following general steps are performed: (a) the medicament is dissolved in an organic solvent to form a solution or suspension; (b) the solution or suspension is sterile filtered; (c) the solution or suspension is either metered into the final use container prior to contact with the supercritical fluid (batch mode) or continuously as a spray with supercritical fluid contact (semi-batch mode); (d) the medicament suspension or solution in the container is contacted with the supercritical fluid until, at a predetermined concentration of supercritical fluid the mixed, expanded liquid is no longer a solvent for the medicament and particle precipitation is effected; (e) the use container is purged with supercritical fluid until the organic solvent is completely depleted from the system; and (f) the finished solid particulate medicament is aseptically sealed in the use container. Thereafter, when it is desired to use the medicament, a liquid carrier may be placed in the use container to form a mixture, which can then be administered by injection or the like.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of the apparatus for the conventional SAS recrystallization from organic solutions.

Fig. 2 is a schematic representation of an apparatus useful in the practice of the invention.

Fig. 3 is a schematic cross-sectional view of the nozzle employed in the practice of the invention.

Fig. 4 is an SEM micrograph (10,000X magnification) of hydrocortisone micronized by recrystallization from a 5 mg/ml DMSO solution using the conventional SAS process with a 100 μm capillary nozzle.

Fig. 5 is an SEM micrograph of hydrocortisone micronized by recrystallization from a 30 mg/ml DMSO solution using the conventional SAS process with a 100 μm capillary nozzle.

Fig. 6 is a GC-FID analysis of hydrocortisone recrystallized from a 30 mg/ml DMSO solution using the conventional SAS process with a 100 μm capillary nozzle.

Figs. 7a and 7b are a pair of SEM micrographs (5,000X and 9,900X magnification, respectively) of hydrocortisone nanonized by recrystallization from a 30 mg/ml DMSO solution using the nozzle of the present invention (compressed CO_2 is used as energizing gas and as antisolvent).

Fig. 8 is an SEM micrograph (3,000X magnification) of hydrocortisone micronized by recrystallization from a 30 mg/ml DMSO solution using the nozzle of

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following Examples set forth techniques, compositions, and system parameters, as well as test results, demonstrating various aspects of the present invention. Examples 1-4 relate primarily to the particle micronization and nanonization aspects of the invention, whereas Examples 5-8 pertain to particle coating; the remaining examples illustrate production of finished products by lyophobic precipitation. It is to be understood, however, that these examples are presented by way of illustration only and that nothing therein should be taken as a limitation upon the overall scope of the invention.

PARTICLE MICRONIZATION AND NANONIZATION

Equipment and Experimental Procedures for Examples 1-4

Fig. 1 shows a schematic of the apparatus 10 used for particle recrystallization from organic solvents using the conventional SAS process. The experimental unit 10 allowed SAS experiments to be conducted in either batch or semi-continuous mode at pressures up to 5,000 psi and temperatures up to 70°C. The mixing of solvent and antisolvent occurred at two different locations 12, 14 within the unit. Unit 10 provided versatility in setting the operating parameters.

The unit 10 was built around a 65 ml high pressure Jerguson gauge (Burlington, MA) view cell 16. The cell 16 was equipped with a sapphire window that allowed viewing of the expansion and crystallization process. The cell 16 was housed in a heated, isothermal, transparent acrylic water bath 18. This water bath 18 was used for maintaining the cell 16 at a desired temperature (20-70°C). When the bath temperature was stable at a desired value, CO_2 was pumped through the top side port 20 of the cell 16 with an ISCO (Lincoln, NE) 260D syringe pump 22 at a constant rate (typically 5 ml/min. of liquid CO_2) until the pressure in the cell 16 reached a desired level (1,500 psi). When temperature and pressure in the cell 16 were stabilized, the organic solution (DMSO or ethyl acetate solution of drug and/or polymer) was metered from the top central port 24 of the cell 16 through a stainless steel, 1/16" O.D., 100 μm I.D. capillary nozzle tubing 26 using a Milton Roy (Riviera Beach, FL) 396-89 minipump 28. It was found that a minimum solution flow rate of 2.5 ml/min. was needed to consistently obtain a jet spray. Both fluids were preheated to operating temperature by passing through heat exchangers 30, 32 housed together with the cell 16 in the water bath 18.

Fresh CO_2 and the organic solution streams mixed at location 14, which is just downstream of the nozzle tip 33 at the top of the cell 16. A cloudy zone about 1 cm long was seen to form in this area indicating intimate mixing of the fluids and particle formation. Solvent depletion from the spray droplets causes the drug and/or polymer

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Fig. 2 shows schematically an apparatus 110 according to the present invention. Apparatus 110 is identical to apparatus 10 with the exception that the view cell serving as crystallization chamber is replaced with a larger (450 ml), stainless steel vessel that can house the nozzle. Here again, the crystallization chamber was housed in an isothermal water bath, and pressure is controlled as described previously with regard to the conventional SAS process (Fig. 1). In apparatus 110, an organic solvent such as dimethyl sulfoxide (DMSO), in which solutes such as drug, polymer, and/or excipient materials are solubilized, is also sprayed as a fine mist into a chamber containing a near-critical or supercritical antisolvent.

In more detail, apparatus 110 of the present invention includes an isothermal and isobaric recrystallization chamber 120, a spray nozzle 124, a source of supercritical (sc) or near-critical (nc) CO_2 126, a source of compressed gas 127 which serves to energize the nozzle 124, a drug and excipient solution 128, an organic solvent collection vessel 156, and a CO_2 outlet header 130.

The drug and excipient solution is drawn from vessel 140 through line 142 by pump 144 and is discharged through line 146 into chamber 120 through line 146 as shown in Fig. 2. The nozzle 124 is attached to the end of line 146 within chamber 120. Energizing gas for the nozzle consisting of He, N_2, O_2, air, CO_2, other supercritical fluids, or a mixture thereof, from source 127 is admitted through line 150 into chamber 120, as shown in Fig. 2. The near-critical or supercritical fluid (antisolvent) is admitted from source 126. Alternatively, if the energizing gas is supercritical (or near-critical), source 127 also can be used for admitting the supercritical fluid into chamber 120; source 126 then may be either not employed, or used for admitting a supercritical fluid in the same composition as in source 124, or a supercritical fluid of different composition. This latter alternative can be used for either increasing or decreasing the concentration gradients between the antisolvent phase and the buffer zone. The solute-depleted organic solvent and solvent-loaded CO_2 are removed from chamber 120 via outlet 122 through line 152 and metering valve 154 into flash drum 156, in which CO_2 is allowed to separate from the liquid organic solvent. The CO_2 is allowed to vent from vessel 156 through vent line 158.

Fig. 3 is a schematic of a nozzle (Sonimist, Farmingdale, N.Y., Model 600-1) employed in apparatus 110. This nozzle N is of the convergent-divergent type and includes a central capillary-type tube T presenting an outlet O. The nozzle N further includes a surrounding passageway P presenting an inlet I for energizing gas. The passageway P includes a converging section C presenting a restricted throat TH and a downstream diverging section D. The section D includes a radially expanded, annular resonator cavity CV. It is to be noted that the outlet O of the tube T is positioned downstream of the throat TH. The nozzle N is energized by compressed gas

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While the above example illustrates conditions under which sonic velocities may be estimated, such high velocities may not be required for all applications. For instance, it has been found that using a chamber pressure of 1,250 psig and an energizing gas pressure of 1,850 psig provides enough energy to reduce particle size

5   substantially. A one order of magnitude reduction in particle size (when compared to results obtained by conventional SAS recrystallization) was also observed when using only 100 psig pressure differential between the chamber held at 1,500 psig and the energizing gas (CO_2). Thus, the nozzle illustrated in Fig. 3 can be used in a wide range of operating conditions in order to substantially reduce particle size and to increase

10   surface area. Broadly speaking, the energizing gas should be delivered to the nozzle N at a pressure of from about 1100-6000 psig, more preferably from about 1500-2500 psig, and at a temperature such that upon expansion, the energizing gas attains the desired temperature of the recrystallization chamber. The frequency of the waves of antisolvent created at the nozzle outlet should be at least about 0.5 kHz and more

15   preferably from about 10-100 kHz.

Furthermore, the invention may be practiced without the use of the nozzle illustrated in Fig. 3. The invention may be practiced with any nozzle that provides a means for using a gaseous (or near-critical or supercritical fluid) stream as energizing medium to atomize the sprayed solution into smaller droplets and/or to create

20   turbulence around the spray droplets which increases the mass transfer rates between the droplet and antisolvent phases. Both converging-diverging nozzles as well as converging nozzles may be employed in the present invention.

<div align="center">Examples 1-4</div>

25   *Comparison of Particles Produced by the Conventional*
SAS Process and the Process of the Present Invention

In these examples, the recrystallization of hydrocortisone, poly (D,L-lactide-glycolide) copolymer (RG503H), ibuprofen, and camptothecin was studied. The recrystallization of hydrocortisone and RG503H was performed using both the

30   conventional SAS process as well as the present invention.

Hydrocortisone is a common anti-inflammatory agent and ibuprofen is a common pain reliever. They were acquired from Sigma Chemical Co., St. Louis, MO, and were used without further purification. Camptothecin is an anti-cancer drug with a very low aqueous solubility; reduction in its particle size or an increase in its particle

35   surface area can substantially increase its dissolution rate and render it therapeutically more useful. RG503H was acquired from Henley, Montvale, N.J. It contains a 1:1 molar ratio of lactide and glycolide and has an inherent viscosity in chloroform of 0.3.

<div align="center">15</div>

Table 1. Reproducibility of Morphology and Size of Particles Formed by the Conventional SAS Recrystallization Method, as Estimated from SEM Micrographs. P = 1,500 psig; CO_2 Flow Rate = 5 ml/min.; Solution Flow Rate = 2.5 ml/min; Capillary Nozzle I.D. = 100 μm.

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Run	Solvent	Solute	Concentration (mg/ml)	Temp. (°C)	Particle Morphology	Average Particle Size (μm)
4-12	DMSO	Hydrocortisone	30	35	Whisker	1
4-14	DMSO	Hydrocortisone	30	35	Whisker	1
4-16	DMSO	Hydrocortisone	30	35	Whisker	1
12-1	Ethyl Acetate	RG503H	10	35	Microsphere	5-50
5-8	Ethyl Acetate	RG503H	10	35	Microsphere	10-20
12-16	DMSO	RG503H	2	35	Tubes/Flakes	25-100
12-20	DMSO	RG503H	2	35	Tubes/Flakes	25-100
6-6	DMSO	HYAFF-7	0.5	40	Resin	>100
6-8	DMSO	HYAFF-7	0.5	40	Resin	>100

Example 1

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Comparison of Results of Recrystallization of Hydrocortisone from DMSO Solutions

Hydrocortisone Particles Produced Using the Conventional SAS Process

Fig. 4 shows the SEM micrograph of hydrocortisone particles recrystallized from a 5 mg/ml DMSO solution using the 100 μm capillary nozzle (P = 1,500 psi; T = 35°C; CO_2 flow rate = 5 ml/min.; solution flow rate = 2.5 ml/min.). Particles are agglomerated, nearly spherical, and range in size from 0.5-1 μm. Recrystallization of hydrocortisone from a 30 mg/ml DMSO solution yielded long (up to 1 mm), 1 μm thick, whisker-shaped particles shown in Fig. 5 (P = 1,500 psi; T = 35°C; CO_2 flow rate = 5 ml/min.; solution flow rate = 2.5 ml/min.; capillary I.D. = 100 μm). Note that the magnification level in the upper part of micrograph (b) is five-fold greater when compared to the lower micrograph. Greater nucleation rates should result at this higher concentration, which should lead to the formation of smaller particles (Gallagher et al., 1989); however, it appears that the increase in viscosity at higher solute concentrations and the premature onset of nucleation, and crystallization prior to secondary atomization hinder the atomization process, resulting in the formation of elongated, whisker-like particles. Indeed, the increase in particle size with an increase in solute

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significant decrease in the average particle size is observed with the use of the present invention.

Hydrocortisone Particles Produced Using the Present Invention in which He Was Used as Energizing Gas and Compressed CO_2 Was Used as Antisolvent

The 30 mg/ml DMSO solution of hydrocortisone was also recrystallized using He at 1,600 psig as energizing gas and CO_2 at 1,500 psig, 35°C as antisolvent. Fig. 8 demonstrates that it is possible to use a light gas to energize the nozzle. Although these conditions are not optimum, the process still produces particles that are relatively small. Some particles appear to be even smaller than 1 μm. The merits of using He as opposed to CO_2 as energizing gas are not evident from Fig. 8; however, it is anticipated that as the solute concentration and viscosity of the solution is increased, it may be necessary to introduce a gaseous buffer such as He to avoid premature nucleation. When using a light gas to energize the nozzle, the flow rate of the supercritical fluid relative to that of the light gas should be high enough to provide sufficient antisolvent power for the supercritical fluid/light gas mixture. Use of CO_2 as both antisolvent and energizing gas, when possible, is advantageous over the use of a light gas as energizing gas because (a) chances for contamination are reduced, (b) the antisolvent power of CO_2 is not diminished, (c) required CO_2 flow rates are lower, and (d) solvent recovery is efficient.

Example 2

Comparison of Results of Recrystallization of RG503H
Particles Produced Using the Conventional SAS Process

RG503H was recrystallized from solutions of DMSO and ethyl acetate at a pressure of 1,500 psig and a temperature of 35°C using a 100 μm capillary nozzle. Neat RG503H particles, as supplied by the vendor, are relatively large, agglomerated precipitates (> 50 μm). Table 2 depicts the effect of RG503H concentration on size and morphology of RG503H recrystallized from solution. RG503H in DMSO appears to recrystallize as tubules at low concentrations, as a mixture of flakes and tubules at medium concentrations, and as precipitates of large amorphous material at higher concentrations.

Pre-mixing of CO_2 with the DMSO solution prior to expansion, aimed at improving mass transfer efficiency, had little effect on particle size and morphology, but caused the formation of bubbles on the surface of the flakes. The formation of relatively large, agglomerated particles at increased polymer concentrations parallel

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*RG503H Particles Produced Using the Present Invention in which Compressed CO$_2$
is used as Energizing Gas and as Antisolvent*

Fig. 10 shows an SEM micrograph of RG503H particles recrystallized from a
10 mg/ml ethyl acetate solution. These particles are compared with particles shown in
5   Figs. 9a and 9b, which are obtained using the conventional SAS process. Both
experiments were conducted at identical conditions of pressure, temperature, and
solution flow rate (1,500 psig, 35°C, and 2.5 ml/min, respectively) within the
crystallization chamber, except that the particles shown in Fig. 10 were obtained using
the present invention in which compressed CO$_2$ was used as energizing gas. The CO$_2$
10   supply pressure was 1,600 psig. Similar to the particles seen in Figs. 9a and 9b, the
RG503H particles in Fig. 10 are also nearly spherical; however, the particles obtained
using the present invention appear more discrete and are an order of magnitude smaller
than particles in Figs. 9a and 9b. As with the results obtained in the previous example,
particle diameter is again narrowly distributed around 1 μm. Thus, the present
15   invention produces smaller particles than the conventional process with less
agglomeration, a property that is desirable, especially in the pharmaceutical industry.

Example 3

*Recrystallization of Ibuprofen from a DMSO Solution Using the Present Invention
in which Compressed CO$_2$ Was Used as Energizing Gas and as Antisolvent*

20   Figs. 11a and 11b show a pair of SEM micrographs of Ibuprofen particles
recrystallized from a 30 mg/ml DMSO solution under the same operating conditions as
in Example 2. Once again, particles appear to be discrete, particle sizes are small and,
except for a fraction of micron-sized particles, most particles are smaller and in the
25   range of 0.6 μm or less.

Example 4

*Recrystallization of Camptothecin from a DMSO Solution
Using the Present Invention is which Compressed CO$_2$
Was used as Energizing Gas and as Antisolvent*

30   Camptothecin, as supplied by the vendor, appears as amorphous particles with
diameters ranging from 1-10 μm. Fig. 12 is an SEM micrograph of camptothecin
particles recrystallized from a 5 mg/ml DMSO solution under the same operating
conditions as in Example 2, (i.e., P = 1,500 psig, 35°C with a CO$_2$ back pressure of
35   roughly 100 psig). Particles are nearly spherical and discrete. Although relatively large

Certified grade ethylacetate and DMSO (99.9% purity, Fisher Scientific, Fairlawn, NJ), bone dry CO_2 (99.8% purity, Genex, Kansas City) were used with no further purification. Recrystallized microparticles were collected on glass beads or nonpareil sugar beads. Particles that deposit on the cell walls were also collected for

5   analysis. Particle morphology and coating uniformity were evaluated by SEM (Hitachi, Model S-570). Particle size was also estimated by SEM. The SEM samples were sputter coated with Au/Pd alloy.

Fig. 14 is a schematic view of a modified view cell used in the Fig. 1 apparatus in the coating experiments. Specifically, the Fig. 1 apparatus was employed except that

10   the modified view cell 16a was used in lieu of the cell 16. The cell 16a in the experiments was equipped with an internal, 16 cm-long, 8 ml glass tube 36a in place of the rod 36 of Fig. 1, a CO_2 extension line 20a leading from port 20 to the bottom of tube 36a, and the capillary nozzle tubing 26a was extended downwardly to a point adjacent the open end of tube 36a.

15   In use, the 16-cm long, 8 ml glass tube 36a is first charged with nonpareil sugar beads or glass beads, and then fitted at the bottom of the view cell as shown in Fig. 14. When the bath temperature is stable at a desired value, CO_2 is pumped through the line 20a at a constant rate (typically 5 mL/min. of liquid CO_2) until pressure in the cell reaches a desired level (1500 psi). When temperature and pressure in the cell are

20   stabilized, the organic solution (DMSO or ethyl acetate solution of drug and/or polymer) is metered through capillary nozzle tubing 26a. Both the organic mixture and CO_2 are preheated to operating temperature by passing through heat exchangers housed together with the cell in the adjacent water bath (see Fig. 1). In order to establish countercurrent flow and fluidize the beads, as described the CO_2 was introduced at the

25   bottom of the tube through port line 20a while the organic solution of the coating material was sprayed from about 2 inches above. It is found that a minimum solution flow rate of 2.5 mL/min. is needed to consistently obtain a jet spray.

Fresh CO_2 and the organic solution streams thus mixed within the glass tube. Solution expansion caused the drug and/or polymer dissolved in the organic solvent to

30   nucleate and the particles to crystallize and descend down the tube.

Recrystallized particles adhered either to the glass tube walls or deposited on the beads. Any particles escaping retention within the view cell chamber were retained on the steel frit housed in the T-shaped fitting at the central bottom port 38 (Fig. 1). A thermocouple inserted through this fitting was used to monitor the cell temperature. the

35   drug/polymer depleted mixture of CO_2 and organic solution flowed through the step-

and CO_2 rate were 100 μm, 35°C, 1500 psig, 2.5 cc/min. and 5 mL/min. of chilled liquid CO_2 respectively.

Fig. 15 is a micrograph of an uncoated nonpareil bead. Figs. 16 and 17 show micrographs of a resulting coated nonpareil bead and glass bead respectively. The nonpareil bead is nearly uniformly coated with a layer of mostly microspheres of RG503H. Coating on the glass bead is less uniform possibly due to its larger size which reduces its mobility within the glass tube. The recrystallized microspheres (Fig. 16) are of similar size (roughly 10 μm) to those obtained in runs at identical conditions with the same solution in the absence of the beads (see Table 1).

In this experiment, constraining of the expansion to within the glass tube and reduction of the efficiency of the atomization process by virtue of pumping the solution into the relatively small volume glass tube caused the solution to expand as a pseudo-liquid phase rather than as microdroplets. The recrystallized polymer microparticles were thus not entrained in the SCF, and were able to coat the beads. As evidence of this observation is the fact that upon removal of the glass tube from the view cell, only the bottom half of the tube visibly contained polymer particles. The upper half, which was not reached by the solution upon expansion appeared polymer-free.

Operation under conditions of higher CO_2 flow rates (25 cc/min. as liquid) to improve the efficacy of the atomization step did eliminate the formation of the expanded liquid phase, but little coating was deposited on the beads due to entrainment of the recrystallized polymer microparticles by the high velocity SCF into the view cell, outside the glass tube, thereby reducing their probability of contacting the beads. Microparticle entrainment away from the region where the core material is confined can be avoided by eliminating the use of the glass tube and loading the core particles into the entire view cell. Alternatively, use of a modified cell approximating a Wurster coater would provide adequate conditions for antisolvent, solution or suspension, and substrate distribution within the coating chamber.

Example 6

Concentration Effects on Coating of Nonpareil Sugar Beads with RG503H

In this study, a solution of 25 mg/ml of RG503H in ethyl acetate was recrystallized under the same conditions as in Example 6. Fig. 18 is an SEM micrograph of a coated nonpareil bead. Coating is less uniform than on beads coated as described in Example 5 using a 10 mg/ml ethyl acetate solution of RG503H. The increase in concentration appears to increase the size of the recrystallized particles and

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electrostatic spraying technique. The instant process also provides an alternative to the Wurster coater technique. Alternatively, the core materials may be tumbled down a conveyor belt disposed in a high pressure CO_2 chamber while a solution or suspension is continuously sprayed on the core materials. Another alternative is to use this process for coating larger objects than drug tablets or pesticide granules. Because recrystallization can occur almost as soon as the spray exits the nozzle in the SAS process, a technique can be employed whereby a nozzle scans the surface of the object, and microparticles are rapidly deposited on the surface upon which the nozzle is spraying the solution. This process could be particularly useful for efficiently painting large surfaces. Another alternative is to coat a large object by merely expanding the solution spray onto a chamber containing the object without necessarily scanning the surface of the object.

Alternatively, adhesives or plasticizers can be added to the organic solution to facilitate adherence of the recrystallized particles to the surface of the substrate or to improve on the physical properties of the coating. Excipients such as colorants may also be added to the organic solution to enhance the aesthetic or functional properties of the coating.

Other Applications for the Coating Method and Apparatus

This invention finds application in all areas where particle coating by recrystallization of the shell material from an organic phase is desirable. These applications can find use, but are not limited to, in coating of: pharmaceutical tablets, granules, pellets or capsules; pesticides; fertilizers; catalysts; seeds; salts; circuit boards; wires, containers and lids.

Antisolvents useful in the application of this invention include, but are not limited to, CO_2, propane, butane, isobutane, CHF_3, SF_6 and N_2O. Organic solvents may be either of the class of aromatic hydrocarbons, alcohols, esters, ethers, ketones, amines, or nitrated or chlorinated hydrocarbons. Preferred solvents include acetone, methanol, ethanol, propanol, isopropanol, dichloromethane, ethyl acetate and DMSO. Blends of these solvents may also be used.

Coating materials useful for this application include sugars, polymers such as poly-lactide glycolide copolymers (PLGA), PLA, PGA, polyvinylpyrrolidone, polyethylene glycols and methacrylic acid ester. The largest group of film forming resins are the cellulose ethers, especially the hydroxypropylmethyl cellulose. Other

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Example 9

Batch precipitation of hydrocortisone from a 200 mg/ml DMSO solution was undertaken. A 1 cc aliquot of solution was pumped into the fritted glass tube positioned inside view cell 16. Pressure and temperature were maintained at 1,575 psig and 31°C.

Twelve standard liters of CO_2 were introduced from the bottom end of the tube and through the frit to expand the solvent and recrystallize the drug. Following this expansion period, 300 standard liters of CO_2 were introduced from the top end of the glass tube to "push" the expanded solution out of the tube through the glass frit and to dry the particles for one hour. This method is attractive because it provides a means for rapidly expanding the solution and recrystallizing the drug, while preventing the solution to expand over the upper rim of the glass tube (or dispensing container).

Example 10

1 mL of a 24.1 mg/mL solution of phenytoin in acetone was transferred into the borosilicate tube. The tube was placed in view cell 16b of Fig 21. The line C_1 extended through the phenytoin solution to the bottom of the borosilicate tube T_u. The cell was quickly pressurized to 800 psig with CO_2 at 40°C through line C_2. It is noted that the CO_2 introduction rate via line C_1 must be sufficiently slow to prevent the forceful ejection of solution. Therefore, initial pressurization can be conducted more quickly using line C_2.

Following initial pressurization, the valve V_2 is closed and CO_2 was introduced through line C_1 at 20 g/min for 9 minutes. The solution expanded and the drug was observed to precipitate. When the expanded solution reached the top of the borosilicate tube the CO_2 flow rate in line C_1 was decreased to 4.5 g/min to minimize drug loss as the expanding solvent overflowed the top of the test tube. After 8 minutes, the pressure within cell 16b reached 1,300 psig. Total CO_2 introduction via bubbling through line C_1 was 200 g. The cell was then depressurized and the borosilicate tube containing product was retrieved.

The precipitated phenytoin (Fig. 22b) was compared to the starting material (Fig. 22a) by Differential Scanning Calorimetry (DSC) and found to exhibit enthalpic transitions consistent with the starting material.

Example 11

1 mL of a 30 mg/mL solution of ibuprofen in DMSO was transferred into the borosilicate tube. The tube was placed in the view cell 16b of Fig 21. Line C_1 extended

We claim:

1.   A process for the precipitation of small particles comprising the steps of:
providing a fluid dispersion including a continuous phase dispersant with at
least one substance to be precipitated dispersed in the dispersant; and
contacting said dispersion with an antisolvent in a precipitation zone at near-or
supercritical conditions for the antisolvent, and causing said substance
to precipitate and form small particles,
said antisolvent being miscible with said dispersant, said substance being
substantially insoluble in the antisolvent,
said contacting step comprising the steps of--
passing said fluid dispersion through a first passageway and first
passageway outlet into said precipitation zone containing said
antisolvent;
passing an energizing gas stream along a second passageway and
through a second passageway outlet proximal to the first outlet,
said passage of said energizing gas stream through said second outlet
generating high frequency sonic waves of said energizing gas
adjacent said first passageway outlet for breaking up said fluid
dispersion into extremely small droplets; and
causing said antisolvent within said precipitation zone to deplete said
dispersant and precipitate small particles of said substance.

2.   The process of claim 1, said dispersion being a solution, said dispersant
being a solvent and said substance being a solute dissolved in said solvent.

3.   The process of claim 1, said conditions during said contacting step being
from about 0.7-1.4 T_c and from about 0.2-7 P_c of said antisolvent.

4.   The process of claim 3, said conditions being from about 1-1.2 T_c and
from about 0.9-2 P_c of said antisolvent.

5.   The process of claim 1, said dispersant and antisolvent being essentially
completely miscible in all proportions thereof.

17.   The process of claim 1, said energizing gas stream having an inherent level of kinetic energy, a substantial portion of said energizing stream kinetic energy being converted to acoustic energy by virtue of said passage of said energizing gas stream through said second outlet.

18.   The process of claim 17, at least about 1% of said inherent kinetic energy being converted to acoustic energy.

19.   The process of claim 1, said energizing gas being selected from the group consisting of air, oxygen, nitrogen, helium, carbon dioxide, propane, butane, isobutane, trifluoromethane, nitrous oxide, sulfur hexafluoride and mixtures thereof.

20.   The process of claim 1, said substance being a medicament.

21.   A process for coating of core particles with a desired substance, said process comprising the steps of:

spraying a fluid dispersion into an enclosed precipitation zone containing a quantity of antisolvent at near-or supercritical conditions for the antisolvent, said fluid dispersion including a continuous phase dispersant with said desired substance dispersed therein, said antisolvent being miscible with said dispersant and said substance being substantially insoluble in the antisolvent;

creating a turbulent fluidized flow of said core particles within said precipitation zone by placing a quantity of said core particles within said precipitation zone and passing a fluidizing gas stream comprising said antisolvent into the precipitation zone; and

causing said antisolvent to deplete said dispersant and precipitate said substance onto said fluidized core particles.

22.   The process of claim 21, said dispersion being a solution, said dispersant being a solvent and said substance being a solute dissolved in said solvent.

23.   The process of claim 21, said conditions during said contacting step being from about 0.7-1.4 T_c and from about 0.2-7 P_c of said antisolvent.

33.   The process of claim 31, including an annular resonator cavity disposed adjacent and in communication with said diverging section.

34.   The process of claim 30, including the step of generating high frequency waves of said energizing gas at a frequency of at least about 0.5 kHz.

35.   The process of claim 34, said frequency being from about 10-100 kHz.

36.   The process of claim 21, including the step of causing said dispersant depletion and particle precipitation so as to obtain particles having an average diameter of from about 0.1-10 μm.

37.   The process of claim 36, said average diameter being up to about 0.6 μm.

38.   The process of claim 30, said energizing gas stream having an inherent level of kinetic energy, a substantial portion of said energizing stream kinetic energy being converted to acoustic energy by virtue of said passage of said energizing gas stream through said second outlet.

39.   The process of claim 38, at least about 1% of said inherent kinetic energy being converted to acoustic energy.

40.   The process of claim 30, said energizing gas being selected from the group consisting of air, oxygen, nitrogen, helium, carbon dioxide, propane, butane, isobutane, trifluoromethane, nitrous oxide, sulfur hexafluoride and mixtures thereof.

41.   The process of claim 21, said fluidizing gas stream having a concentration of said antisolvent therein of at least about 50% by weight.

42.   The process of claim 41, said fluidizing gas stream consisting essentially of said antisolvent.

43.   The process of claim 21, said substance being a medicament.

52.   The process of claim 51, said conditions being from about 1-1.2 T_c and from about 0.9-2 P_c of said antisolvent.

53.   The process of claim 47, said dispersant and antisolvent being essentially
5   completely miscible in all proportions thereof.

54.   The process of claim 47, said dispersant comprising at least about 50% by weight of said dispersion.

10   55.   The process of claim 54, said dispersant comprising at least about 90% by weight of said dispersion.

56.   The process of claim 47, said antisolvent being selected from the group consisting of carbon dioxide, propane, butane, isobutane, nitrous oxide, sulfur
15   hexafluoride and trifluoromethane.

57.   The process of claim 47, including the step of causing said dispersant depletion and particle precipitation so as to obtain particles having an average diameter of from about 0.1-10 μm.
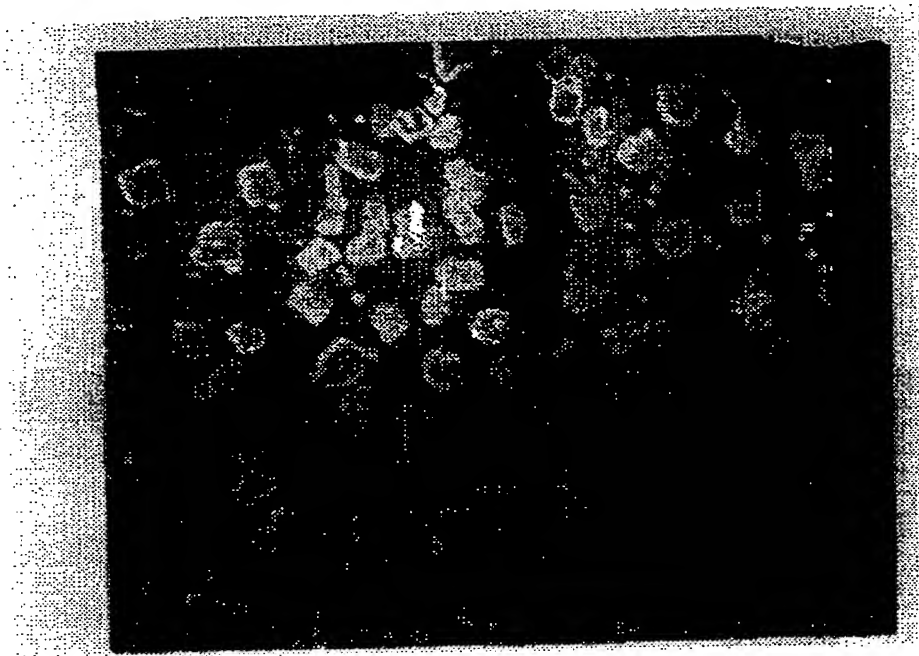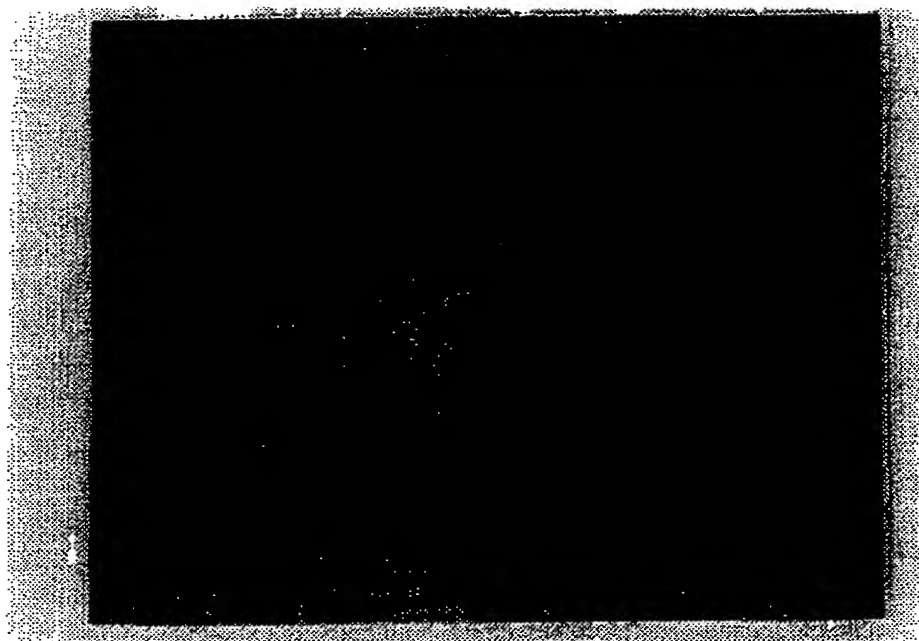
20

Fig.6.

Fig.3.

Solute-loaded
Solvent

Energizing Gas
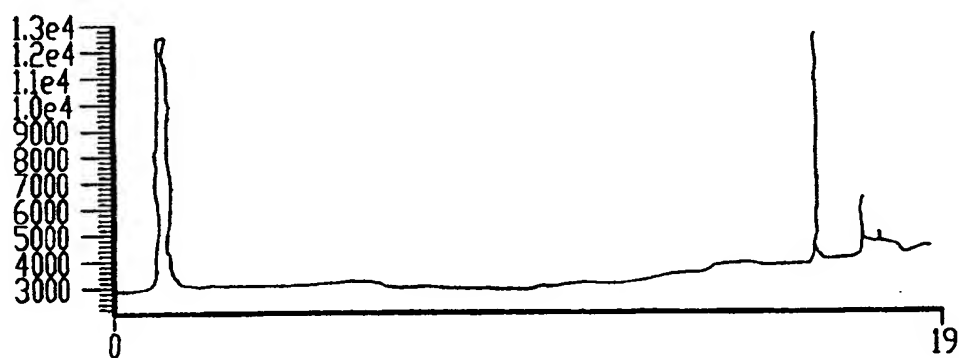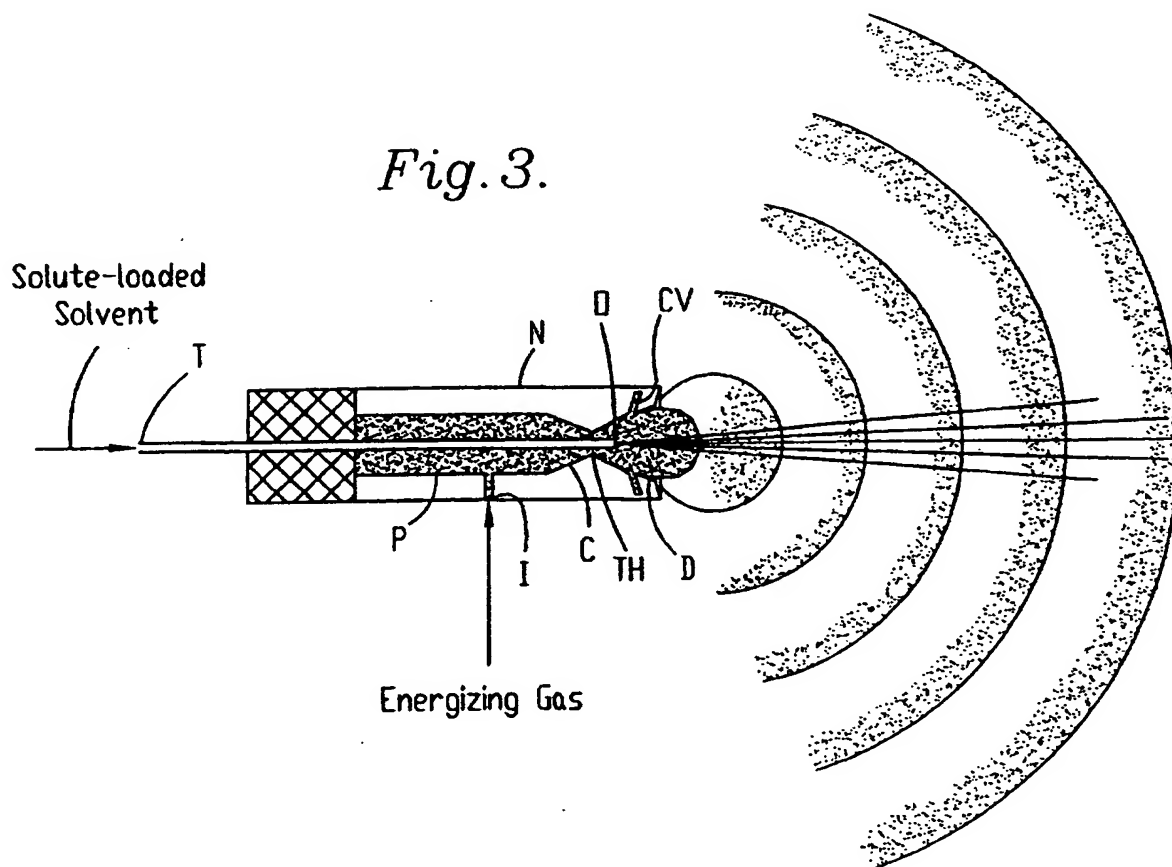
Fig. 7B.

Fig. 7A.
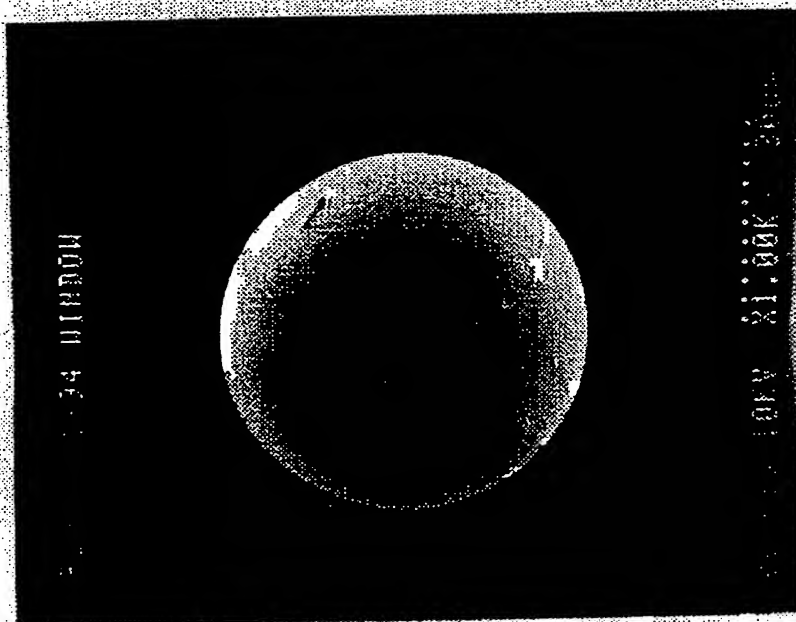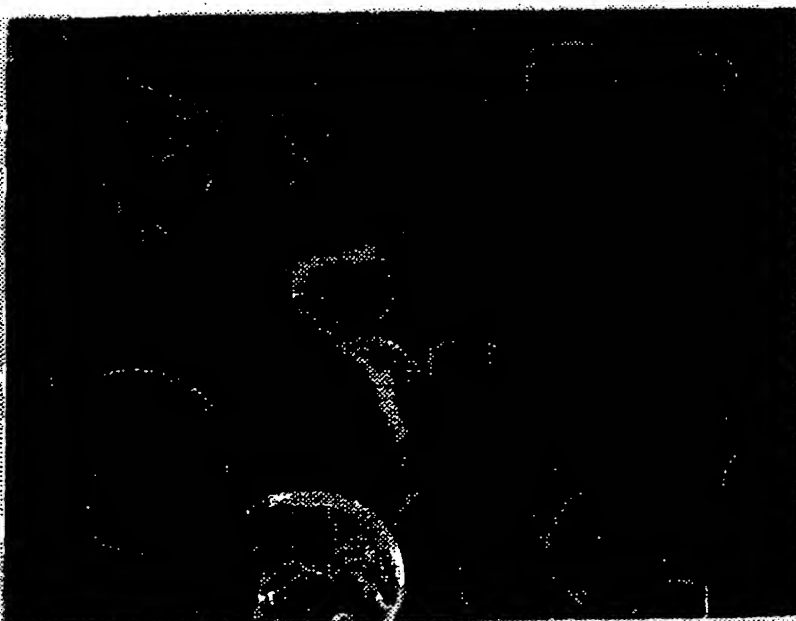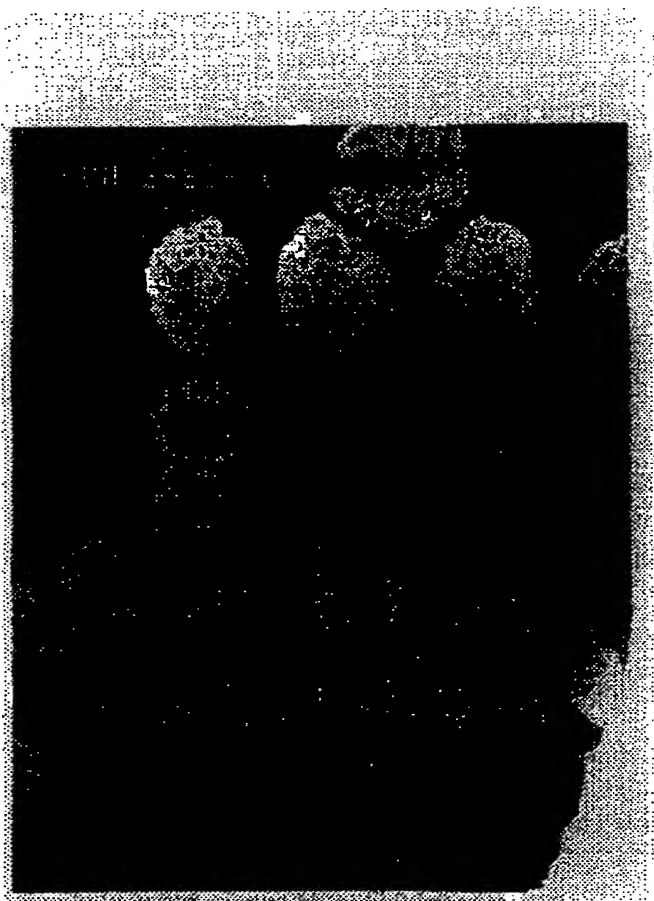
Fig. 9B.

Fig. 9A.

Fig. 12.
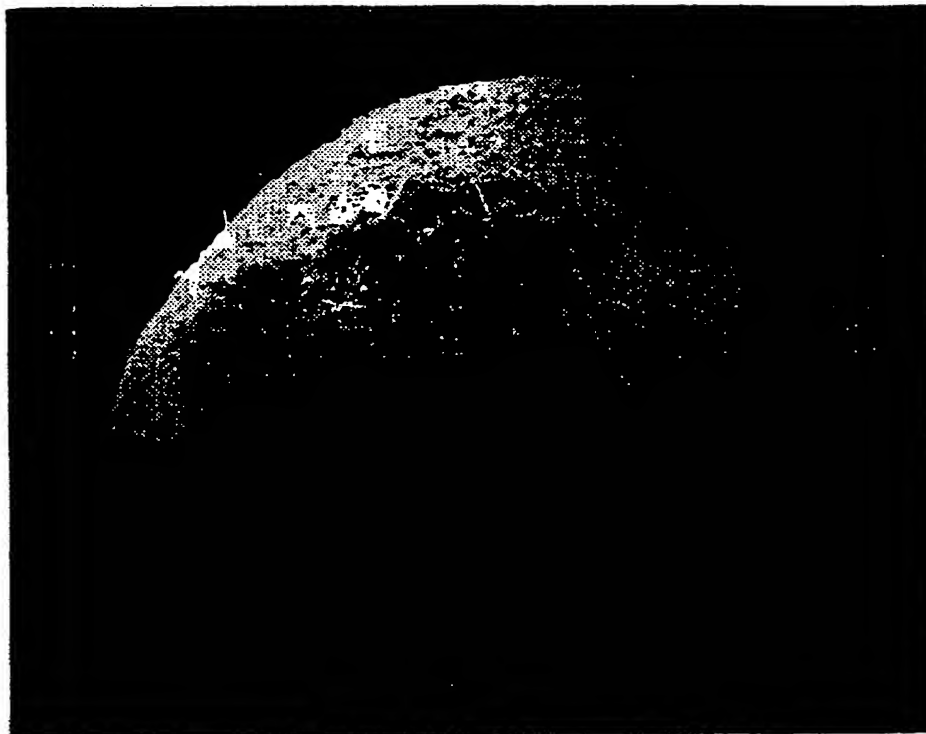
Fig. 16.
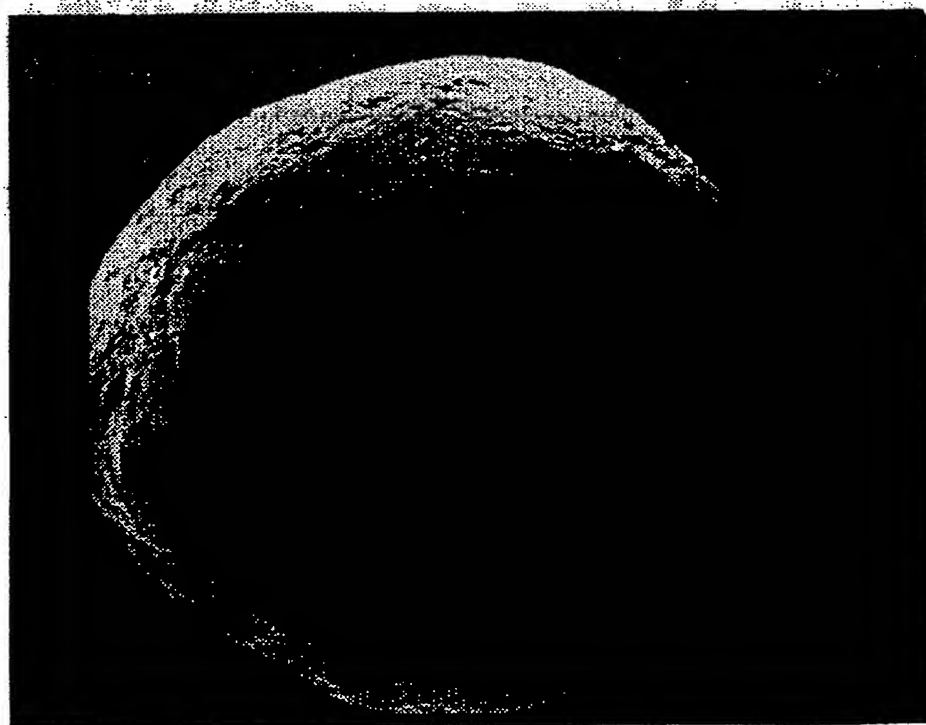
Fig. 15.
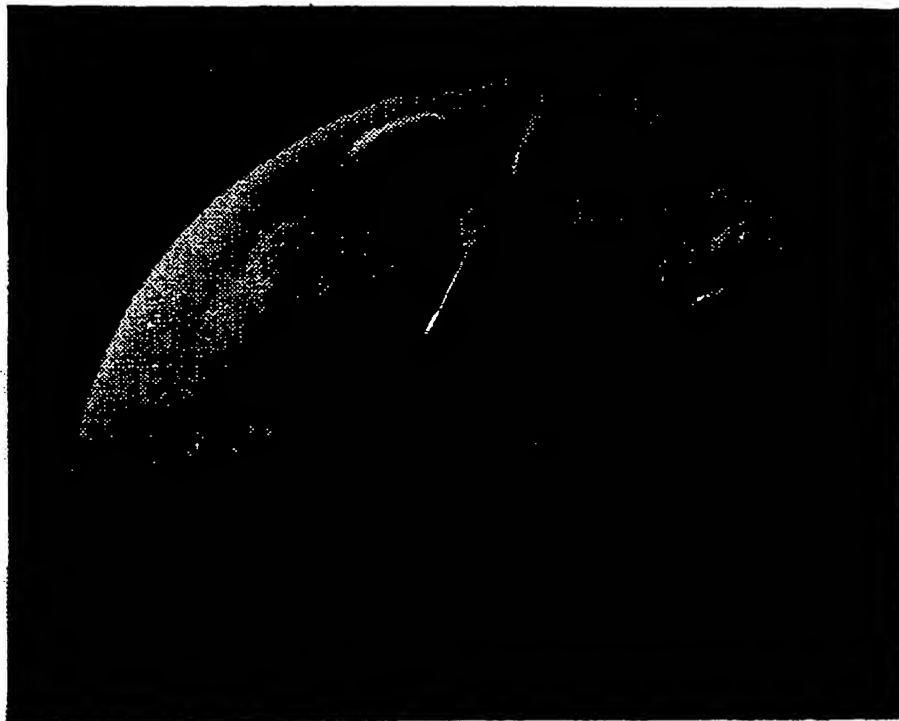
Fig.20.

Fig.19.
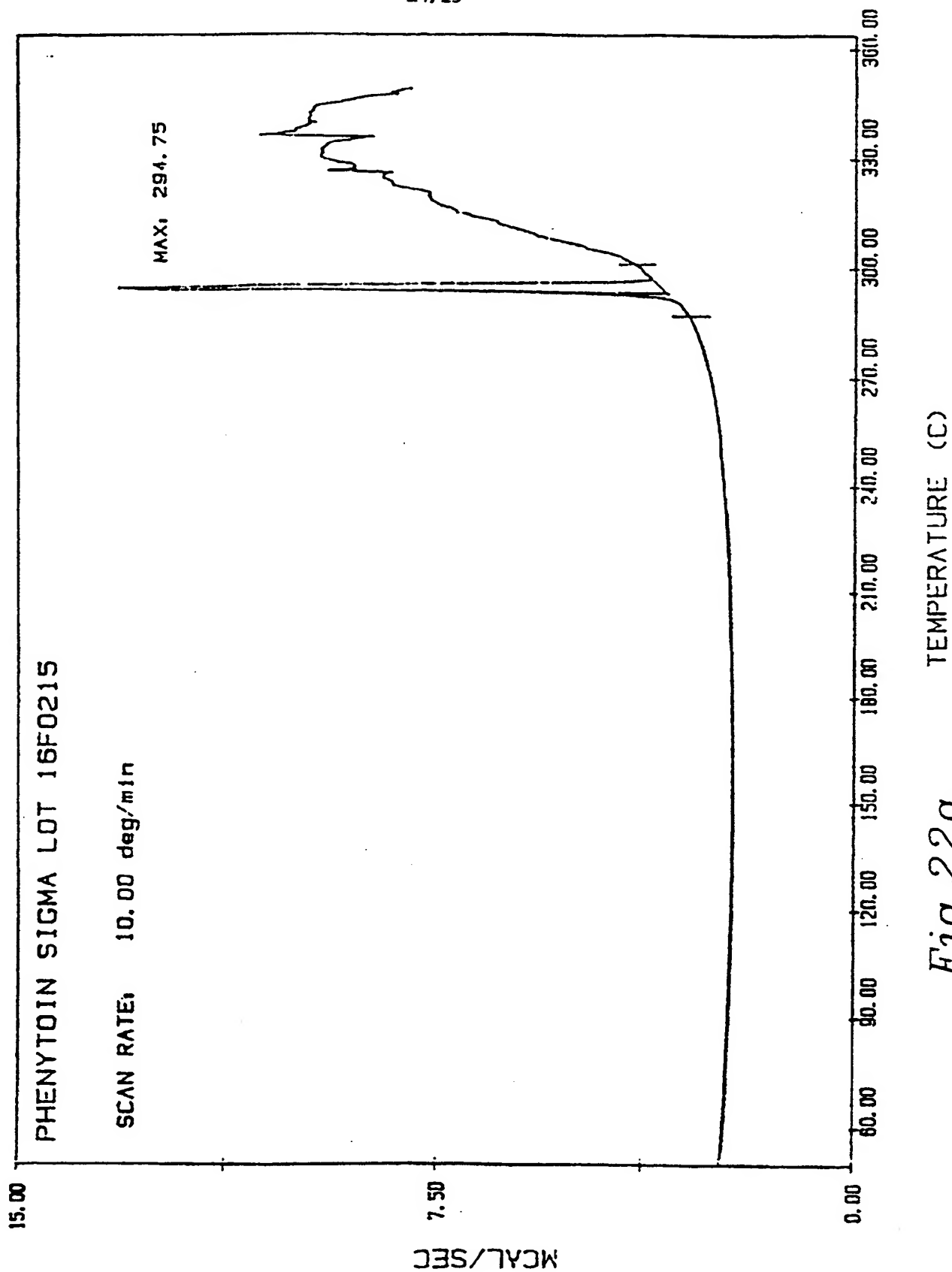
Fig.22a.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :B01B 11/00; B01J 2/04; B05D 1/02

US CL : 264/7,12,13,14; 427/213

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 264/7,12,13,14; 427/213

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,389,263 A (GALLAGHER et al) 14 February 1995 (14.02.95).	1-57
A	US 5,360,478 A 01 (KRUKONIS et al) November 1994 (01.11.94).	1-57
A	US 5,043,280 A (FISCHER et al) 27 August 1991 (27.08.91).	1-57

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	
"E"	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
"O"	document referring to an oral disclosure, use, exhibition or other means	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"P"	document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 MAY 1997	0 9 JUL 1997

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